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**Rhinitis in pregnant women with asthma is associated with poorer asthma control and
quality of life**

Running Head: Rhinitis and asthma in pregnancy

Heather Powell^{1,2}, MMedSc.

Vanessa E Murphy¹, PhD.

Michael J Hensley^{1,2}, PhD.

Warwick Giles^{3,4}, PhD.

Vicki L Clifton⁵, PhD.

Peter G Gibson^{1,2}, MBBS(Hons).

¹Centre for Asthma and Respiratory Diseases, University of Newcastle and Hunter Medical
Research Institute, Newcastle, NSW, Australia.

²Department of Respiratory and Sleep Medicine, John Hunter Hospital, Newcastle, NSW,
Australia.

³University of Sydney, Sydney, NSW, Australia.

⁴Royal North Shore Hospital, Sydney, NSW, Australia.

⁵University of Adelaide, SA, Australia.

Corresponding Author

Heather Powell

Hunter Medical Research Institute

Locked Bag 1000, New Lambton

NSW 2305, AUSTRALIA

Email: heather.powell@hnehealth.nsw.gov.au

Phone: 61 2 40420145; Fax: 61 2 40420001

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ABSTRACT

Objective: To describe the pattern and severity of rhinitis in pregnancy and the impact rhinitis has on asthma control and quality of life in pregnant women with asthma. *Methods:* 218 non-smoking pregnant women with asthma were participants in a randomised controlled trial of exhaled nitric oxide guided treatment adjustment. Rhinitis was assessed using a visual analogue scale (VAS) scored from 0-10 and classified as current (VAS>2.5), moderate/severe vs mild (VAS>6 vs <5), atopic vs non-atopic and pregnancy rhinitis. At baseline, women completed the 20-Item Sino-Nasal Outcome Test (SNOT20), asthma-specific (AQLQ-M) quality of life questionnaires and the Six-Item Short-Form State Trait Anxiety Inventory (STAI-6). Asthma control was assessed using the asthma control questionnaire (ACQ). Perinatal outcomes were collected after delivery. *Results:* Current rhinitis was present in 142(65%) women including 45(20%) women who developed pregnancy rhinitis. Women with current rhinitis had higher scores for ACQ ($p=0.004$), SNOT20 ($p<0.0001$) and AQLQ-M ($p<0.0001$) compared to women with no rhinitis. Current rhinitis was associated with increased anxiety symptoms ($p=0.002$), rhinitis severity was associated with higher ACQ score ($p=0.004$) and atopic rhinitis was associated with poorer lung function ($p=0.037$). Rhinitis symptom severity improved significantly during gestation ($p<0.0001$). There was no impact on perinatal outcomes. Improved asthma control was associated with improvement in rhinitis. *Conclusion:* Rhinitis in pregnant women with asthma is common and associated with poorer asthma control, sino-nasal and asthma-specific QoL impairment and anxiety. In the context of active asthma management there was significant improvement in rhinitis symptoms and severity as pregnancy progressed.

INTRODUCTION

Rhinitis and asthma are the most common medical conditions to complicate pregnancy [1, 2]. In general, 30% of pregnant women have significant nasal symptoms [1] and rhinitis can affect up to 80% of people with asthma [3]. Pregnant women with asthma are at increased risk of adverse perinatal outcomes that may be improved with adequate asthma control [4-6]. Concurrent rhinitis is known to influence asthma control and quality of life among non-pregnant adults [3, 7]. During pregnancy, the course of rhinitis may also predict the course of asthma, improving when asthma improves and worsening with deteriorating asthma as reported in a study subjectively assessing asthma course at the end of the pregnancy [8], although its influence on quality of life in pregnancy is unknown. Current guidelines recommend a stepwise approach to treating rhinitis in pregnancy similar to asthma management [7].

Recent hypotheses suggest rhinitis and asthma are part of the same disease with rhinitis often preceding the development of asthma [9]. Evidence of progressive inflammation from healthy controls to allergic rhinitis to rhinitis and asthma has been demonstrated in previous studies [10-12]. A recent prospective study in non-pregnant adults and older children found, despite provision of topical corticosteroids for asthma and rhinitis, moderate/severe rhinitis was associated with parameters of asthma severity (emergency room visits for acute asthma and poorer asthma control) [13]. To our knowledge there have been no prospective studies to evaluate rhinitis and asthma control in pregnancy.

Our aim was to describe the pattern and severity of rhinitis and the impact rhinitis has on asthma control and quality of life in pregnant women with asthma. We addressed two research questions: 1. In pregnancy and asthma, what impact do rhinitis and rhinitis severity have on asthma and pregnancy outcomes? 2. When asthma treatment is optimised during pregnancy, how does this impact rhinitis?

METHODS

Participants

Pregnant women with a doctor's diagnosis of asthma and symptoms or asthma treatment during the past year were recruited from the John Hunter Hospital antenatal clinic prior to 20 weeks gestation. Participants were non-smoking women in the Managing Asthma in Pregnancy (MAP) Study, a randomised controlled trial (RCT) of exhaled nitric oxide (FENO) vs clinical treatment adjustment in pregnant women with asthma [14]. The study was approved by the Hunter New England Health and University of Newcastle Human Research Ethics Committees and all participants gave informed written consent. The MAP study is registered with the Australian and New Zealand Clinical Trials Registry, number 12607000561482.

Design

Women were seen monthly from study entry to the end of their pregnancy. At each visit asthma control was assessed using the asthma control questionnaire (ACQ) [15], and spirometry and FENO measurements were performed. FENO was measured with online chemiluminescence analysers with 50 mL/s flow rate (ECOMEDICS, Duernten, Switzerland) according to published guidelines from the European Respiratory Society (ERS) and American Thoracic Society (ATS) [16]. At their randomisation/baseline visit (<22 weeks gestation) women completed rhinitis and psychosocial questionnaires[17-19]. Asthma was defined as controlled if the ACQ score <0.75, partially controlled $0.75 \leq \text{ACQ} \leq 1.5$ and uncontrolled $\text{ACQ} > 1.5$ [20]. At baseline women were confirmed as a non-smoker based upon a urinary cotinine measurement <5 (Nicalert: NYMOX Corp. St-Laurent, Quebec, Canada) and exhaled carbon monoxide <10ppm. Women were classified as atopic if they recorded any serum immunoglobulin E (IgE) specific aeroallergen $\geq 0.35 \text{ ku/ml}$.

At each visit the woman's asthma treatment was adjusted according to an algorithm based on either clinical symptoms (Control group) or FENO levels (Intervention group) to up-titrate

(FENO >29ppb) or down-titrate (FENO <16ppb) inhaled corticosteroid (ICS) dosage. Long-acting β_2 -agonist (LABA) and minimum dose ICS were used to treat symptoms when FENO was not elevated. Change in asthma control at end of study was defined as improved (ACQ score decrease >0.5); no change (ACQ score difference <0.5); or worse (ACQ score increase >0.5). Exacerbations were defined by oral corticosteroid use, an unscheduled doctor or emergency department visit or hospitalization for worsening asthma.

Rhinitis assessment

Women were classified as having a past history of rhinitis with asthma if they responded positively when asked if rhinitis triggered their asthma. Rhinitis severity was assessed at monthly visits using a visual analogue scale (VAS). This is a validated method to assess rhinitis severity with a range from 0 (not at all bothersome) to 10 (extremely bothersome) [21]. Women with a VAS score >2.5 at baseline were classified as having current rhinitis. Current rhinitis was further sub-classified by rhinitis severity, atopy and pregnancy rhinitis. A rhinitis VAS score >6 was classified as moderate to severe rhinitis and a VAS score $2.5 < 5$ as mild rhinitis [21]. Women were considered to have atopic rhinitis if they had specific allergen sensitivity ($>0.35\text{kU/L}$) in conjunction with current rhinitis. Pregnancy rhinitis was defined as current rhinitis with no prior history of rhinitis. At baseline women completed the 20-Item Sino-Nasal Outcome Test (SNOT 20) [17]. The SNOT20 questionnaire is a validated outcome measure for rhino-sinusitis with a score range from 0 (low health burden) to 5 (greater health burden). Change in nasal symptoms at end of study was categorised by a clinically significant change in VAS score ≥ 1 [22] (improved: nasal VAS score decrease ≥ 1 ; no change: nasal VAS score difference <1 ; worse: nasal VAS score increase ≥ 1).

Psychosocial Outcomes

Asthma specific quality of life (QoL), was assessed using Asthma Quality of Life Questionnaire- Marks (AQLQ-M) [18]. The AQLQ-M is an asthma specific QoL

questionnaire that measures 20 items across four domains: breathlessness, mood, social, and concerns. Each domain and the total score range from 0-10 with a higher score reflecting poorer quality of life. Anxiety was assessed using the Six-Item Short-Form State Trait Anxiety Inventory (STAI-6) [19], score range 20 (low anxiety) to 80 (high anxiety).

Perinatal Outcomes

Data on perinatal outcomes including delivery, fetal and maternal complications were extracted from the woman's medical records after delivery.

Previously published data from this study include the primary efficacy data from the MAP RCT [14], the relationship between psychosocial outcomes, future exacerbation risk and perinatal outcomes [23] and baseline maternal psychosocial outcomes for a subset of study participants [24]. This analysis is a pre-specified sub study.

Statistical Analysis

Data were analysed using STATA 11 (StataCorp, College Station, Texas, USA). Clinical outcomes, psychosocial questionnaires, SNOT 20 questionnaire scores and perinatal outcomes were analysed by current rhinitis, rhinitis severity, atopic rhinitis and pregnancy rhinitis. Continuous data were analysed by Student's t test or Wilcoxon rank sum test and analysis of variance or Kruskal-Wallis test. Categorical data were analysed using a Chi square or Fisher's exact test. Multivariate logistic regression was performed to determine the association between current rhinitis, asthma control and anxiety. Univariate logistic regression was conducted to determine the ability of nasal VAS score at baseline to predict future exacerbation risk during pregnancy. Change from baseline in nasal VAS score and ACQ score were analysed using generalised linear mixed models. Spearman's correlations were used to assess associations between sino-nasal symptoms and quality of life. A p value<0.05 was considered significant.

RESULTS

The women had a mean (SD) FEV1% predicted=95.57 (13.1), median (1,3Q) ACQ score=0.85 (0.36, 1.14) and 42.7% were on maintenance inhaled corticosteroids (ICS) at baseline. Atopy was present in 75.5% of the women.

Rhinitis

A past history of rhinitis which triggered asthma was reported by 140 (64.5%) women. During pregnancy, current rhinitis was present in 142 (65.1%) of women (70 (65.4%) and 72 (64.9%) for the Control and FENO groups respectively) including 45 (20.6%) who developed pregnancy rhinitis (no prior rhinitis history). No prior history and no current rhinitis were reported by 33 (15%) women (Table 1). Overall, nasal symptoms were moderate with median (1,3Q) nasal VAS score = 4.45 (1.8, 7.2). Eighty two (57.8%) had moderate to severe rhinitis (nasal VAS score>6), and rhinitis was present in 104 out of the 133 women who were atopic (78.2%). The women reported low impact from sino-nasal QoL (SNOT20 mean total score, median (1,3Q) = 0.95 (0.45, 1.63)), asthma specific QoL and anxiety (Table 1).

Current Rhinitis

Women who were currently symptomatic with rhinitis at 20 weeks gestation (current rhinitis) had significantly worse asthma control, reporting a higher ACQ score than those with no current rhinitis 0.86 vs 0.57, $p=0.004$ (Table 2) and a greater proportion of these women were classified as uncontrolled asthma ($ACQ>1.5$, 19.0% vs 13.2%, $p=0.07$). ACQ score remained significantly associated with current rhinitis after adjustment for anxiety, OR (95%CI) 1.62 (1.05, 2.50), $p=0.028$. Women with current rhinitis had mildly impaired quality of life with significantly higher SNOT20 domain and total mean scores (median (1,3Q) 1.30 (0.85, 1.80) vs 0.35 (0.2, 0.7), $p<0.0001$) and higher AQLQ-M scores compared to those without current rhinitis. Women with current rhinitis also experienced greater anxiety compared to those with no current rhinitis (Table 2). The majority of women with current

rhinitis in pregnancy were untreated with only 6 (4.2%) taking antihistamine or nasal corticosteroids.

There were no differences in future asthma exacerbations or perinatal outcomes for those with current rhinitis (Table 2). 72 (33.0%) women had an asthma exacerbation between their baseline visit and the end of their pregnancy. Nasal VAS score at baseline did not predict future exacerbation during pregnancy, OR (95%CI) 1.02 (0.93, 1.12), $p=0.711$.

Rhinitis Severity

Moderate to severe rhinitis (nasal VAS score >6 at baseline; $n=81$, 57.8%) was associated with significantly higher ACQ score ($p=0.004$) and higher FENO ppb ($p=0.043$) at baseline compared to mild rhinitis. Moderate to severe rhinitis was also reflected in significantly higher SNOT20 questionnaire scores and poorer asthma specific quality of life for AQLQ-M mood domain. There were no differences in anxiety scores, exacerbation rates or perinatal outcomes between women with moderate to severe rhinitis and women with mild rhinitis (Table 3).

Atopic Rhinitis

Current rhinitis with atopy was associated with significantly lower lung function (FEV1, $p=0.037$; FEV1/FVC, $p=0.003$), higher FENO ppb ($p<0.0001$) and, as expected, higher specific allergen sensitivity ($p<0.0001$) compared to women with non-atopic current rhinitis (Table 3). There were no differences in QoL, anxiety scores, exacerbation rates or perinatal outcomes between atopic and non-atopic rhinitis.

Impact of improved asthma control on rhinitis in pregnancy

Women with asthma were actively managed with asthma education, asthma skills optimisation, and prescription of maintenance therapy. This led to improved asthma control during pregnancy with lower mean ACQ scores ($p<0.0001$) and increased symptom free days ($p<0.0001$), data not shown. The severity of the women's rhinitis improved as their

pregnancy progressed with only 19.5% experiencing moderate/severe rhinitis at visit 6 (compared to 57.8% at baseline) (figure 1a) and both mild and moderate/severe experiencing a significant improvement in nasal VAS scores (figure 1b). Change in nasal VAS and ACQ score from baseline to their final visit was available in 129 women (figure 2a). Nasal VAS score improved from baseline regardless of the women's change in asthma control, however the improvement was significantly less for those with worse asthma control at the end of the study $p=0.026$ (figure 2b). There was a small but significant correlation between change in nasal VAS score from baseline and change in ACQ score (Spearman's $\rho=0.22$, $p=0.015$). Asthma control was worse in 10 (7.8%) women at their final visit. Rhinitis deteriorated in 6 (4.7%) women with only 1 (10%) of these experiencing worse asthma control at their final visit.

Pregnancy Rhinitis (Table 4)

We compared the characteristics of women with pregnancy rhinitis to women with current rhinitis that included a prior history of rhinitis and those with no rhinitis. At baseline women with pregnancy rhinitis had significantly impaired sino-nasal QoL and asthma specific QoL compared to women with no rhinitis. This impairment was not as severe as those with current rhinitis that included a prior history of rhinitis (Table 4). Women with pregnancy rhinitis had significantly elevated rhinitis symptom scores compared to women with no rhinitis but not as elevated as those with current rhinitis that included a prior history of rhinitis (figure 3a)..

During the pregnancy, rhinitis symptoms improved significantly for both women with current rhinitis and a past history of rhinitis as well as women with pregnancy rhinitis with no significant difference between the two groups.

(figure 3b).

Sino-Nasal Quality of Life

Greater sino-nasal health burden at baseline was significantly correlated to poorer quality of life (AQLQ-M total score) for all women (spearman's $\rho=0.58$, $p<0.0001$) and for women with current rhinitis only (spearman's $\rho=0.58$, $p<0.0001$).

DISCUSSION

The presence of rhinitis was common and mostly untreated with 65% of this group of pregnant women with asthma experiencing current nasal symptoms. In most cases rhinitis was moderate to severe, associated with atopy, and tended to improve during gestation. QoL was impaired in sino-nasal and asthma specific health status assessment, and was associated with increased anxiety symptoms, among women with current rhinitis, whether those with a prior history, or those with pregnancy rhinitis. Rhinitis adversely impacted on asthma control but there was no impact on asthma exacerbations or perinatal outcomes. Controlling asthma led to improvement in rhinitis.

In a study of the impact of rhinitis in people with allergic disease (either asthma and/or rhinitis), rhinitis has been shown to have an impact on both asthma specific QoL and rhinitis specific QoL [25]. Similarly we found that symptomatic rhinitis had a significant impact on all QoL measures. Rhinitis severity was also related to sino-nasal and asthma QoL and poorer asthma control with increased airway inflammation (FENO). Upper and lower airway QoL has been shown to be worse in non-pregnant people with concomitant asthma and rhinitis regardless of their level of asthma control [3].

We found that pregnant women with asthma and atopic rhinitis had lower lung function compared to those with non-atopic rhinitis and asthma. This is consistent with the European Community Respiratory Health Survey which reported an association between atopy and lower lung function in people with asthma [26]. A prospective study conducted in naval personnel with persistent allergic rhinitis without asthma reported an association between duration of allergic rhinitis and house dust mite sensitisation with impaired lung function

[27]. The presence of atopy in conjunction with rhinitis did not confer a greater impact on rhinitis severity, quality of life or asthma control than rhinitis alone. Ponte et al found no difference between atopic and non-atopic people with asthma in rhinitis severity, asthma specific quality of life or uncontrolled asthma in a study of more than 600 people with asthma in Brazil [28]. The higher FENO levels in this group of pregnant women are consistent with a systematic review reporting elevated FENO in healthy adults and children with rhinitis [29]. Rhinitis coexists in 75-80% of people with asthma. The greatest impact of comorbid rhinitis in these women appears to be related to severity which can be modified by adequate treatment. People with comorbid asthma and rhinitis that is treated have fewer hospitalizations than those with untreated rhinitis [30]. The vast majority of our participants were not treated for their rhinitis despite current guideline recommendations for comorbid rhinitis and asthma [7, 30].

Pregnancy rhinitis occurred in 20% of our participants and followed a similar but modified pattern to those with a past history of rhinitis. The reported prevalence of pregnancy rhinitis varies from 9% [31] to 39% [32] with other studies reporting a similar prevalence to the finding from our study [30, 33, 34]. Increased nasal congestion during pregnancy has been attributed to increases in placental growth hormone [34] and increased vascular pooling possibly due to changing levels of oestrogen and progesterone [35]. The increase in nasal congestion can lead to impaired breathing and sleep disturbance which may be detrimental to the fetus [36, 37]. Treatment can include nasal saline washings, nasal dilators and raising the head of the bed [34].

Rhinitis improved along with asthma control as the pregnancy progressed. In fact, rhinitis improved even in the few women where asthma control did not. This is in contrast to a retrospective study in rhinitis and asthma control where rhinitis worsened when asthma worsened [8]. The women in our study all received active asthma management and monthly

review during their pregnancy and were provided with ICS or ICS/LABA therapy as needed.

It is possible, despite few women taking rhinitis treatment, that monitoring the women's asthma closely throughout the pregnancy and providing adequate treatment for asthma control may have concurrently treated the women's rhinitis.

This analysis has some limitations. Using the nasal VAS score to classify rhinitis severity (<5 or >6) excluded 19 people whose nasal VAS was between 5 and 6 from the rhinitis severity analysis. Women with non-symptomatic rhinitis (nasal VAS score <2.5) were included in the 'no current rhinitis' group. In addition, the SNOT 20 questionnaire has not been validated to assess rhinitis quality of life. However, in this group of pregnant women with asthma, we have demonstrated that sino-nasal QoL as assessed by the SNOT20 questionnaire was related to symptomatic rhinitis.

CONCLUSION

Rhinitis in pregnant women with asthma is common and is associated with poorer asthma control, sino-nasal and asthma specific QoL impairment and anxiety but not adverse perinatal outcomes. Controlling asthma with active asthma management was associated with a significant improvement in rhinitis symptoms and severity as pregnancy progressed.

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Declaration of Interest

The authors declare no conflict of interest

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Table 1.**Subject Characteristics at baseline**

N	218
Age, years ^α	28.45 (5.44)
Gestational age, weeks*	20 (18.5, 21)
BMI*	28.52 (24.09, 32.66)
FEV1/FVC ^α	0.80 (0.07)
FEV1% predicted ^α	95.57 (13.12)
FVC% predicted ^α	104.25 (14.12)
ACQ score *	0.85 (0.36, 1.14)
FeNO*	13.3 (7.38, 26.1)
Atopy ^β	154 (75.49%)
B2-agonist use in past week, days used*	2 (0, 6)
Maintenance ICS ^β	93 (42.66%)
BDP equivalent ICS dose (mcg per day)*	800(400, 800)
Rhinitis treatment (antihistamine/nasal spray)*	9 (4.13%)
<i>Rhinitis</i> ^β	
Nasal VAS score, cm	4.45 (1.8, 7.2)
Current rhinitis (nasal vas>2.5)	142 (65.14%)
Pregnancy rhinitis	45/142 (31.69%)
Rhinitis triggers asthma	140 (64.52%)
Rhinitis severity during pregnancy:	
Mild	41/142 (28.9%)
Mod/Severe	82 (57.8%)

Unclassified (VAS 5≤6)	19 (13.4%)
<i>Psych variables</i> *	N=209
SNOT20 Rhinologic domain	1.4 (0.6, 2.27)
SNOT 20 Ear/Facial domain	0.38 (0, 1.0)
SNOT 20 Psych domain	0.67 (0.17, 1.5)
SNOT20 mean total score	0.95 (0.45, 1.63)
AQLQM Total score	0.88 (0.38, 1.63)
STAI-6 Total score	26.67 (20, 36.67)
<i>Perinatal outcomes at end of study</i>	N=212
Birth weight, g*	3500 (3060, 3880)
Low birth weight (<2500gms)	9/209 (4.31%)
Preterm delivery	14 (6.6%)
IUGR	4 (1.89%)
Neonatal hospitalization	25 (11.79%)

* Median (1,3Q); [†] n(%); BDP: beclomethasone; BMI: body mass index; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; ACQ: asthma control questionnaire; FENO: fraction of exhaled nitric oxide; VAS: visual analogue scale; SNOT 20: Sino-Nasal Outcomes test; AQLQ-M: Asthma Quality of Life Questionnaire-Marks; STAI-6: Six-Item Short-Form State trait Anxiety Inventory; IUGR: Intrauterine growth restriction.

Table 2: Characterisation at baseline by baseline rhinitis

	No Current Rhinitis	Current Rhinitis	P value
n	76	142	
age ^α	27.61 (5.46)	28.80 (5.40)	0.094
FEV1/FVC ^α	0.80 (0.07)	0.80(0.07)	0.840
FEV1% predicted ^α	97.04 (13.23)	94.77 (13.05)	0.226
FVC% predicted ^α	106.02 (14.43)	103.30 (13.91)	0.176
ACQ score*	0.57 (0.28, 1.0)	0.86 (0.43, 1.29)	0.004
Asthma control ^β			0.070
Controlled (ACQ<0.75)	44 (57.89%)	59 (41.55%)	
Partial control (ACQ>=0.75<=1.5)	22 (28.95%)	56 (39.44%)	
Uncontrolled (ACQ>1.5)	10 (13.16%)	27 (19.01%)	
Exacerbation after baseline and during pregnancy ^β	23 (30.26%)	49 (34.75%)	0.503
FeNO ppb*	10.5 (6.56, 22.80)	14.65 (7.8, 29.9)	0.103
Atopy ^β	50(70.42%)	104 (78.20%)	0.219
B2-agonist use in past week (days)	1 (0, 5.5)	2 (0, 6)	0.067
Maintenance ICS ^β	30 (39.47%)	63 (44.37%)	0.486
BDP equivalent ICS dose (mcg per day)*	800 (400, 1600)	800 (400, 800)	0.944
Rhinitis treatment (antihistamine/nasal spray) ^{β#}	3 (3.95%)	6 (4.23%)	1.0
Antihistamine ^{β#}	2 (2.6%)	2 (1.4%)	0.612
Nasal corticosteroid ^{β#}	1 (1.3%)	4 (2.8%)	0.660

<i>Rhinitis*</i>			
Nasal VAS score	1.1 (0.2, 1.8)	6.6 (4.5, 8.0)	<0.0001
<i>Psych variables*</i>	N=91	N=165	
SNOT20 Rhinologic domain	0.6 (0.2, 0.8)	1.8 (1.2, 2.6)	<0.0001
SNOT 20 Ear/Facial domain	0 (0, 0.5)	0.5 (0.25, 1.25)	<0.0001
SNOT 20 Psych domain	0.17 (0, 0.5)	1.0 (0.33, 1.67)	<0.0001
SNOT20 mean score	0.35 (0.2, 0.7)	1.30 (0.85, 1.80)	<0.0001
AQLQM breathlessness	1 (0, 1.5)	1.5 (0.5, 2.5)	0.003
AQLQM Mood	1 (0.5, 2)	2(1, 3)	<0.0001
AQLQM Concerns	0 (0, 0.36)	0.36 (0, 1.07)	<0.0001
AQLQM Social	0 (0, 0.36)	0 (0, 0.71)	0.001
AQLQM Total score	0.63 (0.25, 1.13)	1.06 (0.5, 1.75)	<0.0001
STAI-6 Total score	23.3 (20.0, 30.0)	30.0 (20.0, 36.67)	0.002
<i>Immunology*</i>	N=71	N=133	
Total IgE IU/ml,	88 (23, 191)	93 (37, 239)	0.470
House dust KuA/ml	1.89 (0.13, 19.7)	8.48 (0.31, 34.0)	0.055
Mould KuA/ml	0.05 (0.03, 0.19)	0.05 (0.03, 0.11)	0.497
Weed KuA/ml	0.06 (0.04, 0.14)	0.07 (0.04, 0.23)	0.454
Domestic mix KuA/ml	0.11 (0.02, 1.18)	0.16 (0.03, 1.05)	0.822
Grass mix KuA/ml	0.11 (0.01, 2.81)	0.13 (0.01, 1.38)	0.787
<i>Perinatal outcomes at end of study</i>	N=76	N=136	
Birth weight, g*	3387.5 (3020, 3714)	3515 (3100, 3920)	0.124
Low birth weight (<2500gms) [#]	6/74 (8.11%)	3/135 (2.22%)	0.070
Preterm delivery ^β	7 (9.21%)	7 (5.15%)	0.253

IUGR#	1 (1.32%)	3 (2.21%)	1.0
Neonatal hospitalization ^β	9 (11.84%)	16 (11.76%)	0.987

* Median (1,3Q), Wilcoxon rank sum test; ^α Mean(SD), Student's t test; ^β n(%), Chi square test, [#] Fisher's exact test; BDP: beclomethasone; BMI: body mass index; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; ACQ: asthma control questionnaire; FENO: fraction of exhaled nitric oxide; VAS: visual analogue scale; SNOT 20:Sino-Nasal Outcomes test; AQLQ-M: Asthma Quality of Life Questionnaire-Marks; STAI-6: Six-Item Short-Form State Trait Anxiety Inventory; IUGR: Intrauterine growth restriction.

Table 3: Rhinitis characterisation at baseline by rhinitis severity and atopy

	Mild Rhinitis	Mod/Severe Rhinitis	P Value	Non-atopic	Atopic	P Value
n	41	82		29	104	
FEV1/FVC ^a	0.80 (0.08)	0.80 (0.07)	0.905	0.83 (0.05)	0.79 (0.07)	0.003
FEV1% predicted ^a	93.13 (12.23)	94.87 (13.19)	0.483	99.53 (10.66)	93.76 (13.60)	0.037
FVC % predicted ^a	101.25 (11.71)	103.48 (14.59)	0.397	104.54 (12.27)	103.61 (14.35)	0.750
ACQ score*	0.57 (0.42, 1.0)	1.0 (0.71, 1.57)	0.004	0.86 (0.42, 1.0)	0.85 (0.43, 1.57)	0.260
FENO ppb*	10.04 (6.1, 26.0)	15.75 (8.5, 29.9)	0.043	6.6 (5.1, 10.7)	17.85 (9.85, 36.75)	<0.0001
Atopy ^β	26/37 (70.27%)	63/77 (81.82%)	0.163	0	104 (100%)	0
B2-agonist use in past week (days)*	1 (0, 5)	3 (1, 7)	0.069	2 (0, 4)	2 (0, 7)	0.457
Maintenance ICS ^β	16 (39.02%)	37 (45.12%)	0.520	14 (48.3%)	45 (43.3%)	0.631
BDP equivalent	800 (400, 800)	800 (400, 800)	0.942	800 (400, 800)	800 (400, 800)	0.463
ICS dose (mcg per day)*						
Exacerbation after baseline and during pregnancy ^β	14 (34.15%)	26 (32.10%)	0.820	10 (35.7%)	36 (34.6%)	0.914
<i>Rhinitis*</i>						

Nasal VAS score	3.5 (3, 4.2)	7.65 (7.0, 8.7)	<0.0001	5.5 (4.2, 7.5)	6.75 (4.9, 8)	0.235
<i>Psych variables*</i>	N=39	N=75		N=28	N=99	
SNOT20	1.2 (0.6, 1.8)	2.4 (1.6, 3)	<0.0001	1.6 (1.2, 2.2)	2.2(1.2, 2.8)	0.067
Rhinologic domain			1			
SNOT 20	0.5 (0, 1.0)	0.75 (0.25, 1.25)	0.009	0.75 (0.25, 1)	0.75 (0.25, 1.25)	0.703
Ear/Facial domain						
SNOT 20 Psych domain	0.67 (0.17, 1.17)	1.17 (0.5, 1.83)	0.009	1 (0.33, 1.67)	1 (0.33, 1.67)	0.581
SNOT20 mean score	0.85 (0.5, 1.45)	1.55 (1.0, 2.05)	<0.0001	1.3 (0.5, 1.8)	1.4 (0.9, 1.8)	0.354
AQLQM breathlessness	1.5 (0.5, 2)	1.5 (0.5, 3)	0.275	1.25 (0.5, 2.5)	1.5 (0.5, 2.5)	0.700
AQLQM Mood	1.5 (1, 2.5)	2.5 (1.0, 3.0)	0.049	2.0 (1, 3.5)	2 (1, 3)	0.705
AQLQM Concerns	0.36 (0, 0.71)	0.36 (0, 1.43)	0.099	0.36 (0, 0.07)	0.36 (0, 1.07)	0.253
AQLQM Social	0 (0, 0.54)	0.36 (0, 0.71)	0.061	0 (0, 0.71)	0.36 (0, 0.71)	0.157
AQLQM Total score	0.88 (0.5, 1.63)	1.23 (0.63, 1.94)	0.099	1.0 (0.5, 1.75)	1.13 (0.63, 1.75)	0.427
STAI-6 Total score	26.67 (20, 36.67)	30 (20, 36.67)	0.379	33.3 (23.3, 40)	26.67 (20, 36.67)	0.10
<i>Immunology, *</i>	N=38	N=76				
Total IgE IU/ml,	91 (28, 188)	94 (43,287)	0.335	8 (3.5, 18)	150.5 (63, 333)	<0.0001

					317)	
House dust kU/L	5.04 (0.13, 21.7)	10.8 (0.34, 36.5)	0.391	0.01 (0.01, 0.03)	13.7 (4.14, 41.2)	<0.0001
Mould kU/L	0.04 (0.03, 0.14)	0.05 (0.03, 0.13)	0.316	0.03 (0.02, 0.05)	0.06 (0.04, 0.17)	<0.0001
Weed kU/L	0.07 (0.04, 0.18)	0.07 (0.04, 0.240)	0.887	0.04 (0.03, 0.05)	0.09 (0.05, 0.3)	<0.0001
Domestic mix kU/L	0.1 (0.01, 0.82)	0.22 (0.03, 1.26)	0.230	0.01 (0, 0.03)	0.27 (0.08, 1.59)	<0.0001
Grass mix kU/L	0.05 (0.01, 0.77)	0.25 (0.01, 2.17)	0.158	0.01 (0.01, 0.02)	0.39 (0.03, 2.24)	<0.0001
<i>Perinatal outcomes at end of study</i>	N=41	N=77		N=28	N=99	
Birth weight, g*	3535 (3310, 3920)	3495 (3100, 3890)	0.396	3508 (3160, 3810)	3495 (3040, 3910)	0.778
Low birth weight (<2500gms) [#]	1/41 (2.44%)	1/76 (1.32%)	1.0	0	3 (3.1%)	1.0
Preterm delivery [#]	2 (4.88%)	3 (3.90%)	1.0	1 (3.6%)	6 (6.1%)	1.0
IUGR [#]	1 (2.44%)	2 (2.60%)	1.0	2 (7.1%)	1 (1.0%)	0.122
Neonatal hospitalization [#]	2 (4.88%)	10 (12.99%)	0.212	2 (7.1%)	14 (14.1%)	0.520

* Median (1,3Q), Wilcoxon rank sum test; ^a Mean(SD), Student's t test; ^b n(%), Chi square test, [#] Fisher's exact test; BMI: body mass index; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; ACQ: asthma control questionnaire; FENO: fraction of exhaled nitric oxide; VAS: visual analogue scale; SNOT 20:Sino-Nasal Outcomes test;

AQLQ-M: Asthma Quality of Life Questionnaire-Marks; STAI-6: Six-Item Short-Form State trait Anxiety Inventory; IUGR: Intrauterine growth restriction.

Table 4. Characterisation by Rhinitis History

	No Rhinitis	Current and Prior Rhinitis	Current Pregnancy Rhinitis	P value
n	N=76	N=97	N=45	
ACQ score	0.57 (0.28, 1.0)	0.95 (0.57, 1.29) [¥]	0.85 (0.29, 1.28)	0.009
FeNO ppb	10.5 (6.56, 22.8)	15.3 (8.3, 29.9)	12.8 (6.7, 25.2)	0.183
Atopy ^β	50 (70.4%)	75 (82.42%)	29 (69.05%)	0.117
B2-agonist use in past week, days used	1 (0, 5.5)	3 (0, 7) [¥]	1 (0, 4) [¥]	0.008
Maintenance ICS ^β	30 (39.47%)	45 (46.39%)	18 (40.0%)	0.607
BDP equivalent ICS dose (mcg per day)	800 (400, 1600)	800 (400, 80)	800 (400, 800)	0.828
Exacerbation after baseline and during pregnancy ^β	23 (30.26%)	36 (37.11%)	13 (29.55%)	0.540
<i>Rhinitis</i>				
Nasal VAS score	1.1 (0.2, 1.8)	7.0 (5.0, 8.0) [¥]	5.1 (4.0, 7.3) [¥]	0.0001
<i>Psych variables*</i>	N=75	n=91	N=43	
SNOT20 Rhinologic domain	0.6 (0.2, 0.8)	2.0 (1.2, 2.8) [¥]	1.8 (1.2, 2.4) [¥]	0.0001
SNOT 20 Ear/Facial domain	0 (0, 0.5)	0.75 (0.25, 1.0) [¥]	0.5 (0, 1.5) [¥]	0.0001
SNOT 20 Psych domain	0.17 (0, 0.50)	1.17 (0.3, 1.67) [¥]	0.75 (0.33, 1.5) [¥]	0.0001
SNOT20 mean score	0.35 (0.2, 0.7)	1.45 (0.9, 1.8) [¥]	1.1 (0.65, 1.75) [¥]	0.0001
AQLQM breathlessness	1.0 (0, 1.5)	1.5 (0.5, 2.5) [¥]	1.5 (0.5, 2.5)	0.009

AQLQM Mood	1.0 (0.5, 2.0)	2.0 (1.0, 3.0) [¥]	2.0 (1.0, 2.5) [¥]	0.0001
AQLQM Concerns	0 (0, 0)	0.36 (0, 1.07) [¥]	0.36 (0, 0.71) [¥]	0.0002
AQLQM Social	0 (0, 0.36)	0.36 (0, 0.71) [¥]	0 (0, 0.7)	0.005
AQLQM Total score	0.63 (0.25, 1.13)	1.25 (0.5, 1.75) [¥]	1.0 (0.5, 1.63) [¥]	0.0001
STAI-6 Total score	23.3 (20.0, 30.0)	30.0 (20.0, 36.67)	30.0 (20.0, 40.0)	0.009
[¥]				
<i>Perinatal Outcomes at end of study</i>	n=74	N=91	N=44	
Birth weight, g*	3388 (3020, 3714)	3520 (3200, 4000)	3495 (3040, 3875)	0.385
Low birth weight (<2500gms) [#]	6 (8.1%)	3 (3.3%)	0	0.107
Preterm delivery [#]	7 (9.21%)	6 (6.52%)	1 (2.27%)	0.371
IUGR [#]	1 (1.32%)	2 (2.17%)	1 (2.27%)	1.0
Neonatal hospitalization	9 (11.84%)	12 (13.04%)	4 (9.09%)	0.823

*Numbers are Median (IQR), Kruskal-Wallis test; ^a Mean(SD), analysis of variance; ^b n(%),

Chi square test [#] Fisher's exact test. [¥] post hoc test significant vs no Rhinitis. ; BMI: body mass index; FENO: fraction of exhaled nitric oxide; VAS: visual analogue scale; SNOT 20:Sino-Nasal Outcomes test; AQLQ-M: Asthma Quality of Life Questionnaire-Marks; STAI-6: Six-Item Short-Form State trait Anxiety Inventory; IUGR: Intrauterine growth restriction.

Figure 1. a) Rhinitis severity at each monthly visit for women with current rhinitis, b) Mean (SD) Nasal VAS score by rhinitis severity at baseline. VAS: visual analogue scale.*
 $p < 0.0001$ Mild vs Moderate/Severe.

Figure 2. a) Change from baseline to final visit in ACQ score and nasal VAS score for women with current rhinitis. b) Change from baseline in mean nasal VAS score for women with improved, no change and worse asthma control at end of study. * Bonferroni post hoc test $p = 0.04$ vs improved asthma control, ACQ: asthma control questionnaire, VAS: visual analogue scale.

Figure 3. Pregnancy rhinitis. a) Median nasal VAS score at 20 weeks gestation: * Kwallis2 post hoc test $p < 0.0001$ vs no rhinitis. b) Mean nasal VAS score for rhinitis and pregnancy rhinitis. VAS: visual analogue scale. # Improvement from baseline for rhinitis and pregnancy rhinitis, $p < 0.000$, no difference between groups, $p > 0.05$.

Fig 1

a)

b)

Fig 2

Fig 3